



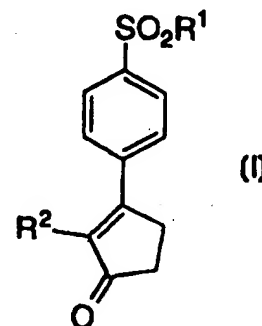
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(54) Title: PYRIDINYL-2-CYCLOPENTEN-1-ONES AS SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

(57) Abstract

The invention encompasses the novel compound of Formula (I) as well as a method of treating COX-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula (I). The invention also encompasses certain pharmaceutical compositions for treatment of COX-2 mediated diseases comprising compounds of Formula (I).



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- 1 -

TITLE OF THE INVENTION**PYRIDINYL-2-CYCLOPENTEN-1-ONES AS SELECTIVE
CYCLOOXYGENASE-2 INHIBITORS****5 BACKGROUND OF THE INVENTION**

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

Non-steroidal, antiinflammatory drugs exert most of their
10 antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive
15 enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the COX-1 which has been cloned, sequenced
20 and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the
25 constitutive enzyme, COX-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, COX-2, is mainly responsible for the pathological
30 effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of COX-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition

- 2 -

would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

Furthermore, such a compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for the treatment of glaucoma.

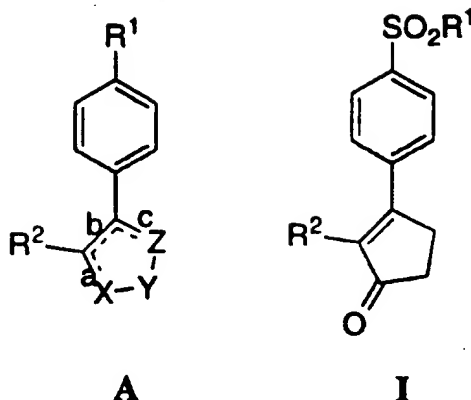
The potential utilities of selective cyclooxygenase-2 inhibitors are discussed in the following articles:

- 1. John Vane, "Towards a better aspirin" in Nature, Vol. 367, pp. 215-216, 1994
- 2. Bruno Battistini, Regina Botting and Y.S. Bakhle, "COX-1 and COX-2: Toward the Development of More Selective NSAIDs" in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.
- 3. David B. Reitz and Karen Seibert, "Selective Cyclooxygenase Inhibitors" in Annual Reports in Medicinal Chemistry, James A. Bristol, Editor, Vol. 30, pp. 179-188, 1995.

United States Patent 5,474,995 (December 12, 1995) and World Patent Application 95/00501 (January 5, 1995) disclose compounds represented by Formula A as being useful in the treatment of COX-2 mediated diseases, by virtue of their selective inhibition of COX-2 rather than COX-1. We have now discovered that a subset of the compounds represented by A, in which -X-Y-Z- is -C(O)CH₂CH₂- and R² is pyridinyl or substituted pyridinyl show unexpectedly superior selectivity for the inhibition of COX-2 over COX-1 and/or superior potency as compared to the closest species disclosed in 95/00501. This subset of compounds is the subject of the present invention and is

- 3 -

represented by Formula I.

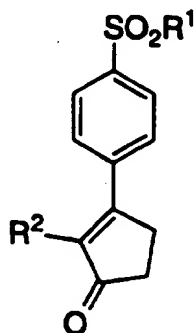


Of the 150-plus specific compounds disclosed in U.S. Patent
 5 5,474,995 and World Patent Application 95/00501 only 10 of them are
 cyclopentenones, and none of these latter is a pyridinyl cyclopentenone.
 Furthermore, among the variety of specific compounds disclosed, only
 one of them contains a heterocyclic group in the place of R², and that
 group is quinoline, not pyridine.

10

SUMMARY OF THE INVENTION

The invention encompasses the novel compound of Formula
 I as well as a method of treating COX-2 mediated diseases comprising
 administration to a patient in need of such treatment of a non-toxic
 15 therapeutically effective amount of a compound of Formula I.



I

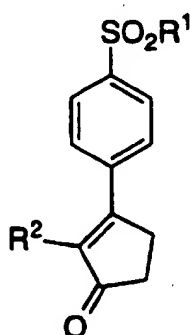
The invention also encompasses certain pharmaceutical
 compositions for treatment of COX-2 mediated diseases comprising

- 4 -

compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

- The invention encompasses the novel compound of Formula I as well as a method of treating COX-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I



I

10

wherein:

R¹ is selected from the group consisting of

- (a) CH₃,
(b) NH₂,
(c) NHC(O)CF₃,
(d) NHCH₃;

15

R² is a mono-, di-, or tri-substituted pyridinyl, wherein the substituents are chosen from the group consisting of

20

- (a) hydrogen,
(b) halo,
(c) C₁-6alkoxy,
(d) C₁-6alkylthio,

25

- (e) CN,
(f) C₁-6alkyl,
(g) C₁-6fluoroalkyl,

- 5 -

- (h) N₃,
- (i) -COOR³,
- (j) hydroxy,
- (k) -C(R³)(R⁴)-OH,
- 5 (l) -C₁₋₆alkyl-CO₂-R³,
- (m) C₁₋₆fluoroalkoxy;

R³ and R⁴ are independently chosen from the group consisting of

- (a) hydrogen,
- (b) C₁₋₆alkyl,

10 or R³ and R⁴ together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

A preferred sub-generic structure of compound I is that wherein R² is a mono-, di-, or trisubstituted 2-pyridinyl, and the remainder of the
15 substituents are as described for I.

Another preferred sub-generic structure of compound I is that wherein R² is a mono-, di-, or trisubstituted 3-pyridinyl, and the remainder of the substituents are as described for I.
20

Yet another preferred embodiment of structure I is that wherein R¹ is CH₃ or NH₂.

Another preferred embodiment of structure I is that wherein the
25 substituents on R² are chosen from the group consisting of

- (a) hydrogen,
- (b) halo,
- (c) C₁₋₆alkoxy,
- (d) C₁₋₆alkylthio,
- 30 (e) C₁₋₆alkyl,
- (f) CF₃,
- (g) CN.

The following abbreviations have the indicated meanings:

35

- 6 -

	AA	=	arachidonic acid
	Ac	=	acetyl
	AIBN	=	2,2'-azobisisobutyronitrile
	BHT	=	butylated hydroxytoluene
5	Bn	=	benzyl
	dba	=	dibenzylideneacetone
	DMAP	=	4-(dimethylamino)pyridine
	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethyl sulfoxide
10	EDTA	=	ethylenediaminetetraacetic acid
	Et ₃ N	=	triethylamine
	HBSS	=	Hanks balanced salt solution
	HEPES	=	N-[2-Hydroxyethyl]piperazine-N ¹ -[2-ethanesulfonic acid]
15	HWB	=	human whole blood
	KHMDS	=	potassium hexamethyldisilazane
	LDA	=	lithium diisopropylamide
	LPS	=	lipopolysaccharide
	MMPP	=	magnesium monoperoxyphthalate
20	Ms	=	methanesulfonyl = mesyl
	MsO	=	methanesulfonate = mesylate
	NBS	=	N-bromosuccinimide
	NCS	=	N-chlorosuccinimide
	NIS	=	N-iodosuccinimide
25	NMP	=	N-methylpyrrolidone
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
	PEG	=	polyethyleneglycol
30	Ph	=	phenyl
	r.t.	=	room temperature
	rac.	=	racemic
	Tf	=	trifluoromethanesulfonyl = triflyl
	TfO	=	trifluoromethanesulfonate = triflate

- 7 -

	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography
	Ts	=	p-toluenesulfonyl = tosyl
	TsO	=	p-toluenesulfonate = tosylate
5	Tz	=	1H (or 2H)-tetrazol-5-yl
	SO ₂ Me	=	methyl sulfone
	SO ₂ NH ₂	=	sulfonamide

Alkyl group abbreviations

10	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
	n-Bu	=	normal butyl
15	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
	c-Pr	=	cyclopropyl
	c-Bu	=	cyclobutyl
20	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

Dose Abbreviations

	bid	=	bis in die = twice daily
25	qid	=	quater in die = four times a day
	tid	=	ter in die = three times a day

For purposes of this specification alkyl is defined to include linear, branched and cyclic structures, with the indicated number of carbon atoms. Examples of alkyl are methyl, ethyl, propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclohexylmethyl and the like. Similarly, alkoxy and alkylthio mean linear, branched and cyclic structures, with the indicated number of carbon atoms.

- 8 -

For purposes of this specification fluoroalkyl means alkyl groups of the indicated number of carbon atoms in which one hydrogen or more is replaced by fluorine. Examples are -CF₃, -CH₂CH₂F, -CH₂CF₃, c-Pr-F₅, c-Hex-F₁₁ and the like. Similarly, fluoroalkoxy
5 means linear, branched and cyclic structures, with the indicated number of carbon atoms.

For purposes of this specification, in situations in which a term occurs two or more times, the definition of the term in each occurrence is independent of the definition in each additional
10 occurrence.

For purposes of this specification halo means F, Cl, Br, or I.

In another embodiment, the invention encompasses
15 pharmaceutical compositions for inhibiting COX-2 and for treating COX-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and non-toxic therapeutically effective amount of a compound of formula I as described above.

In yet another embodiment, the invention encompasses a
20 method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:
administration to a patient in need of such treatment of a non-toxic
25 therapeutically effective amount of a compound of Formula I as disclosed herein.

Optical Isomers - Diastereomers - Geometric Isomers

30 Some of the compounds described herein contain one or more asymmetric centres and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts

- 9 -

thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

5

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, N-methylglucamine, glucamine, glucosamine, histidine, hydrabamine, N-(2-hydroxyethyl)piperidine, N-(25 (2-hydroxyethyl)pyrrolidine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, adipic, aspartic, 1,5-naphthalenedisulfonic, benzenesulfonic, benzoic, camphorsulfonic, citric, 1,2-ethanedisulfonic, ethanesulfonic, ethylenediaminetetraacetic, fumaric, glucoheptonic, gluconic, glutamic,

- 10 -

hydriodic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, 2-naphthalenesulfonic, nitric, oxalic, pamoic, pantothenic, phosphoric, pivalic, propionic, salicylic, stearic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, undecanoic, 10-undecenoic, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, methanesulfonic, phosphoric, sulfuric and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumour growth and hence can be used in the treatment of cancer. Compound 1 may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for treatment of glaucoma.

By virtue of its high inhibitory activity against COX-2 and/or its specificity for COX-2 over COX-1, compound I will prove useful as an alternative to conventional NSAID'S, particularly where

- 11 -

such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anaemia such as
5 hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Pharmaceutical Compositions

For the treatment of any of these cyclooxygenase mediated diseases compound I may be administered orally, topically, parenterally,
10 by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such
15 as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating COX-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

20 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according
25 to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the
30 active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn

- 12 -

starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the
5 gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for
10 control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed
15 with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous
20 suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with
25 fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products
30 of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, benzyl alcohol, one or more colouring agents, one or more flavouring agents, and one or more

- 13 -

sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The
5 oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

10 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already
15 mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for
20 example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example
25 polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and
30 flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also

- 14 -

be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

- 5 Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the
10 preparation of injectables.

- Compound of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at
15 the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

- For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth
20 washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Dose Ranges

- Dosage levels of the order of from about 0.01 mg to about
25 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about
30 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral

- 15 -

administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between
5 from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors
10 including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Combinations with Other Drugs

15 Similarly, compound of Formula I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating COX-2 mediated diseases as
20 defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H₂-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including
25 phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol:
30 a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated ~~diseases comprising: administration to a patient in need of such~~ treatment a non-toxic therapeutically effective amount of the compound of Formula I, optionally co-administered with one or more of such

- 16 -

ingredients as listed immediately above.

Methods of Synthesis

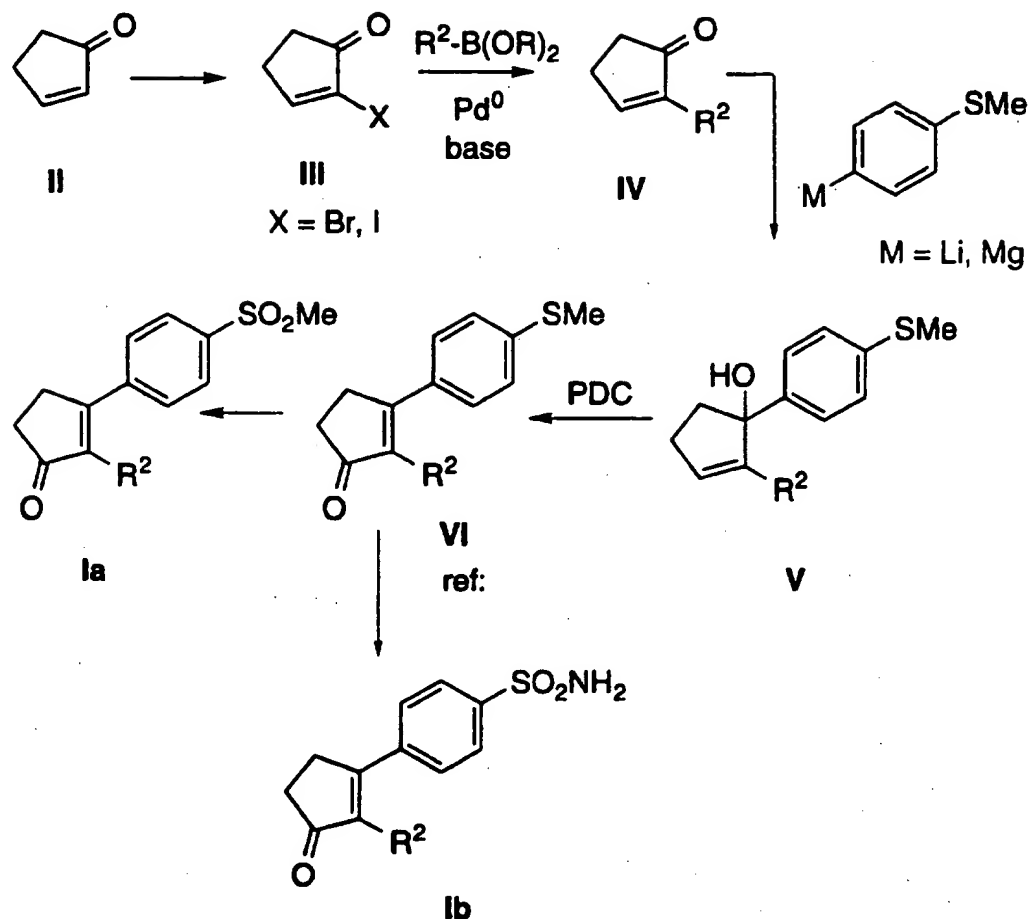
- 5 The compounds of the present invention can be prepared according to the following methods.

Method A

- Cyclopentenone (II) may be halogenated with bromine or iodine followed by treatment with a base to give III (see Organic
10 Syntheses 61 65). An appropriately substituted pyridine boronic acid may then be added via a palladium-catalyzed coupling reaction to form IV. 4-Bromothioanisole may be metalated with nBuLi or magnesium, and then treated with IV to give the alcohol V. Oxidation with allylic transposition may then be accomplished using an oxidant such as PDC to
15 give cyclopentenone VI. Sulfide oxidation using an oxidant such as MMPP or mCPBA then provides sulfone Ia. Alternatively, VI may be converted to sulfonamide Ib as described in U.S. Patent 5,474,995.
-

- 17 -

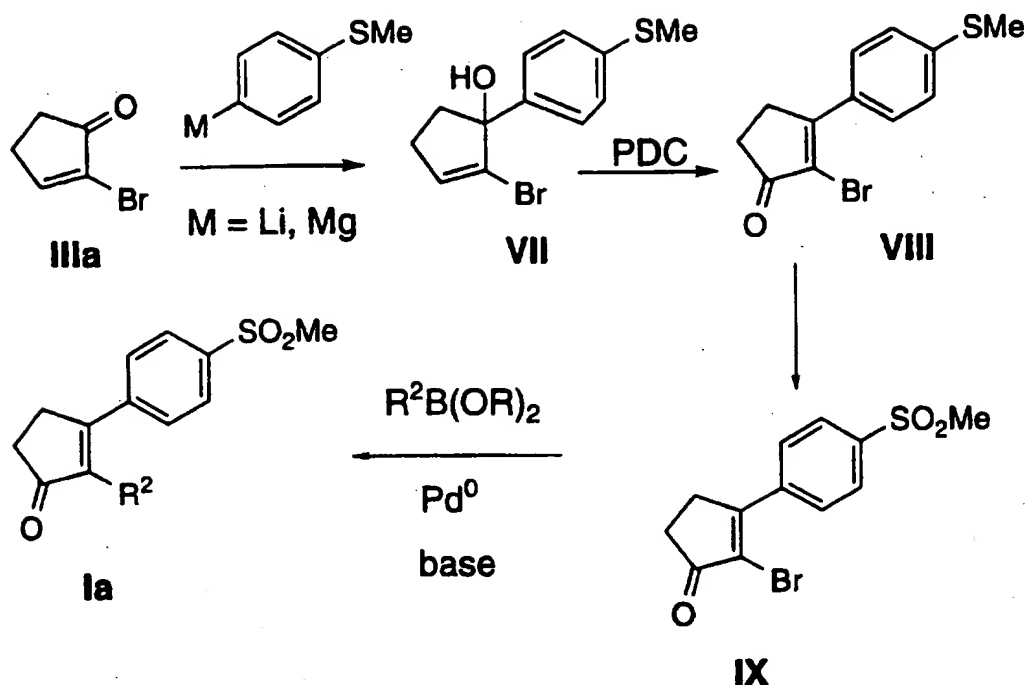
Method A:



Method B

- 5 To bromocyclopentenone **IIIa** is added lithio or magnesium thioanisole to give tertiary alcohol **VII**. Oxidation with a reagent such as PDC then provides the ketone **VIII**. The sulfide may be oxidized at this point using an oxidant such as MMPP or mCPBA to give the sulfone **IX**. Palladium-catalyzed coupling of an appropriately substituted
- 10 pyridinyl boronic acid then provides **Ia**.

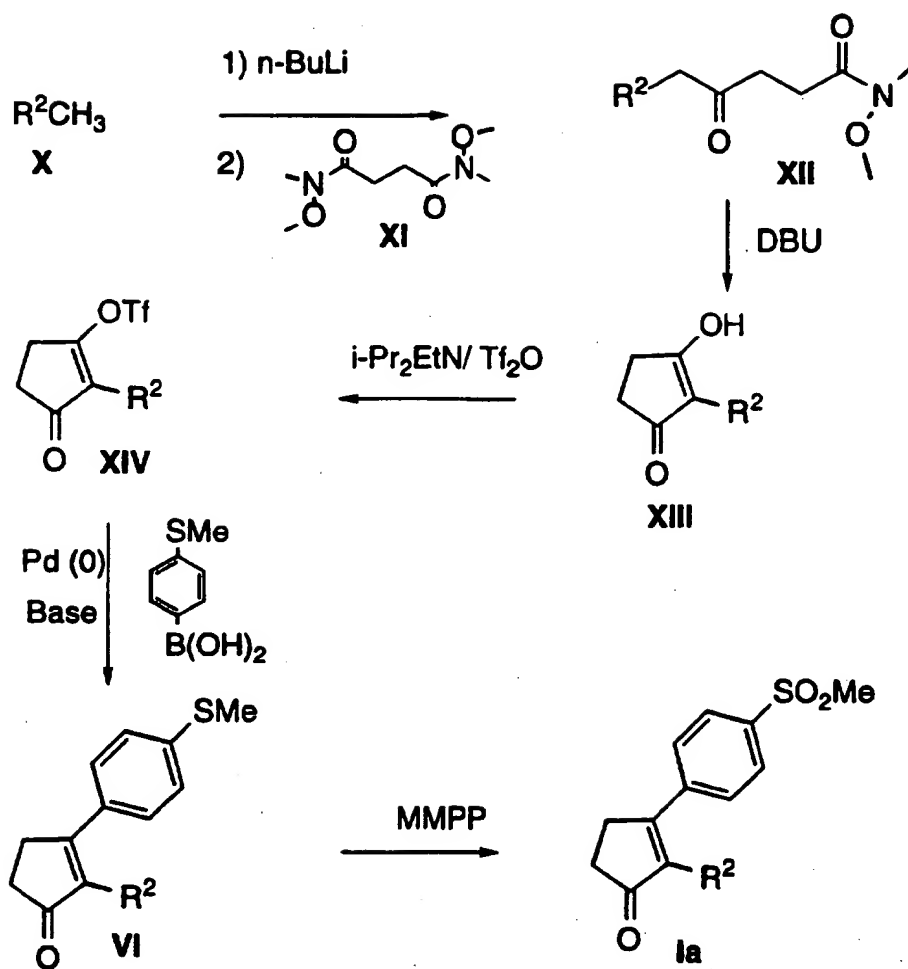
- 18 -



Method C

- An appropriately substituted methylpyridine **X** may be
- 5 deprotonated with an alkyl lithium reagent and the resulting anion added to a diamide **XI** to provide the ketoamide **XII**. Cyclization of this intermediate with a base such as DBU provides the enol **XIII** which can then be converted to the triflate **XIV**. A palladium-catalyzed coupling reaction with 4-(methylthio)phenylboronic acid in the presence of an
 - 10 appropriate base then provides sulfide **VI** which can be oxidized to give the sulfone **Ia** or the sulfonamide **Ib** as described in Method A.

- 19 -



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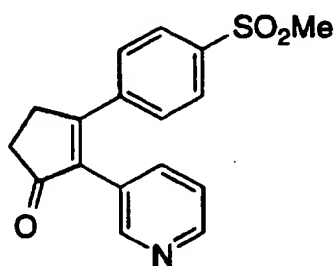
Representative Compounds

Table I illustrates compounds of formula I, which are representative of the present invention.

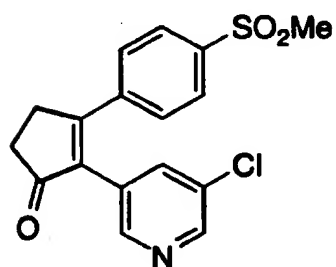
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Table I

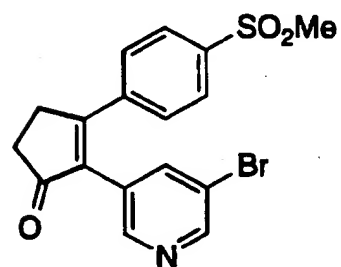
EXAMPLE



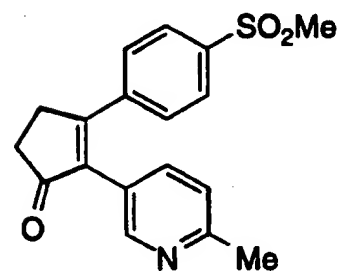
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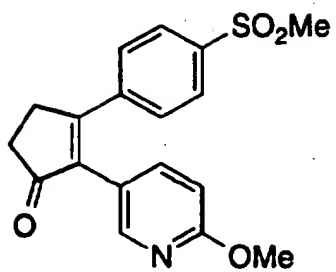


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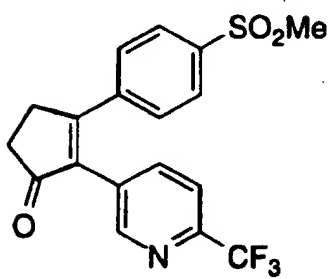


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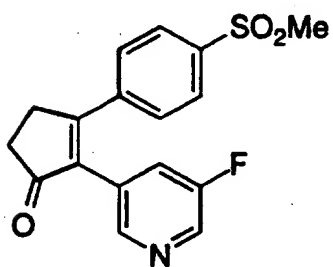
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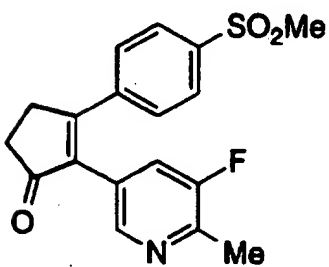
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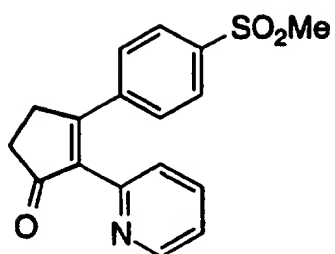
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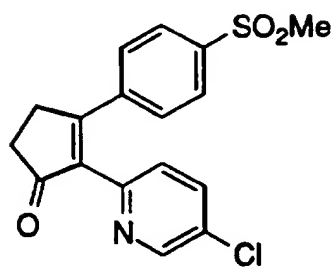
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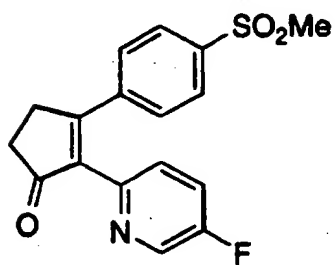
EXAMPLE



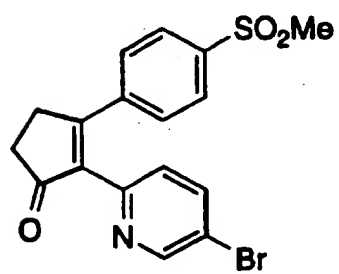
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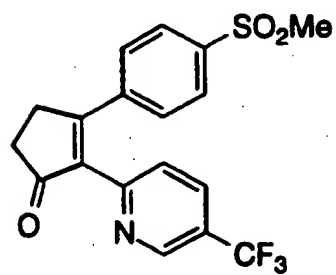
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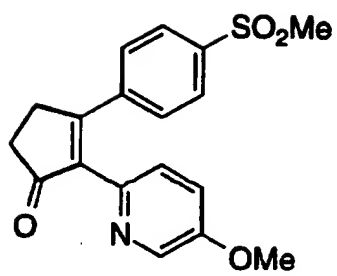


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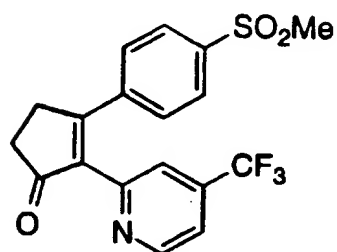


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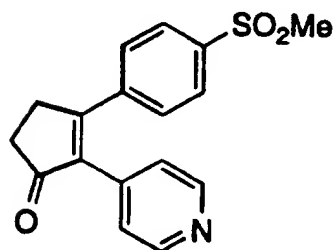
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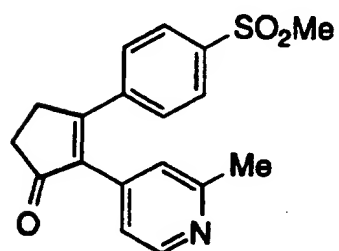
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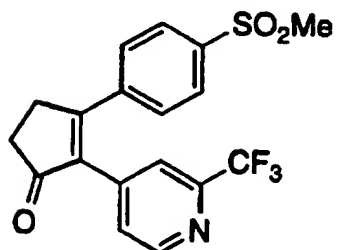
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- 24 -

Assays for Determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their COX-2 inhibiting activity.

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INHIBITION OF CYCLOOXYGENASE ACTIVITY

Compounds are tested as inhibitors of cyclooxygenase activity in whole cell cyclooxygenase assays. Both of these assays measure prostaglandin E₂ synthesis in response to AA, using a radioimmunoassay. Cells used for these assays are human osteosarcoma 143 cells (which specifically express COX-2) and human U-937 cells (which specifically express COX-1). In these assays, 100% activity is defined as the difference between prostaglandin E₂ synthesis in the absence and presence of arachidonate.

15

Whole Cell Assays

For cyclooxygenase assays, osteosarcoma cells are cultured in 1 mL of media in 24-well multidishes (Nunc) until confluent ($1-2 \times 10^5$ cells/well). U-937 cells are grown in spinner flasks and resuspended to a final density of 1.5×10^6 cells/mL in 24-well multidishes (Nunc). Following washing and resuspension of osteosarcoma and U-937 cells in 1 mL of HBSS, 1 μ L of a DMSO solution of test compound or DMSO vehicle is added, and samples gently mixed. All assays are performed in triplicate. Samples are then incubated for 5 or 15 minutes at 37°C, prior to the addition of AA. AA (peroxide-free, Cayman Chemical) is prepared as a 10 mM stock solution in ethanol and further diluted 10-fold in HBSS. An aliquot of 10 μ L of this diluted solution is added to the cells to give a final AA concentration of 10 μ M. Control samples are incubated with ethanol vehicle instead of AA. Samples are again gently mixed and incubated for a further 10 min. at 37°C. For osteosarcoma cells, reactions are then stopped by the addition of 100 μ L of 1N HCl, with mixing and by the rapid removal of the solution from cell monolayers. For U-937

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- 25 -

cells, reactions are stopped by the addition of 100 μ L of 1N HCl, with mixing. Samples are then neutralized by the addition of 100 μ L of 1N NaOH and PGE₂ levels measured by radioimmunoassay.

5 Whole cell assays for COX-2 and COX-1 using CHO transfected cell lines

Chinese hamster ovary (CHO) cell lines which have been stably transfected with an eukaryotic expression vector pCDNAIII containing either the human COX-1 or COX-2 cDNA's are used for the
10 assay. These cell lines are referred to as CHO [hCOX-1] and CHO [hCOX-2], respectively. For cyclooxygenase assays, CHO[hCOX-1] cells from suspension cultures and CHO[hCOX-2] cells prepared by trypsinization of adherent cultures are harvested by centrifugation (300 x g, 10 min) and washed once in HBSS containing 15 mM HEPES, pH
15 7.4, and resuspended in HBSS, 15 mM HEPES, pH 7.4, at a cell concentration of 1.5×10^6 cells/ml. Drugs to be tested are dissolved in DMSO to 66.7-fold the highest test drug concentration. Compounds are typically tested at 8 concentrations in duplicate using serial 3-fold serial dilutions in DMSO of the highest drug concentration. Cells (0.3×10^6
20 cells in 200 μ L) are preincubated with 3 μ L of the test drug or DMSO vehicle for 15 min at 37°C. Working solutions of peroxide-free AA (5.5 μ M and 110 μ M AA for the CHO [hCOX-1] and CHO [COX-2] assays, respectively) are prepared by a 10-fold dilution of a concentrated AA solution in ethanol into HBSS containing 15 mM
25 HEPES, pH 7.4. Cells are then challenged in the presence or absence of drug with the AA/HBSS solution to yield a final concentration of 0.5 μ M AA in the CHO[hCOX-1] assay and a final concentration of 10 μ M AA in the CHO[hCOX-2] assay. The reaction is terminated by the addition of 10 μ L 1 N HCl followed by neutralization with 20 μ L of 0.5
30 N NaOH. The samples are centrifuged at 300 x g at 4°C for 10 min, and an aliquot of the clarified supernatant is appropriately diluted for the determination of PGE₂ levels using an enzyme-linked immunoassay for PGE₂ (Correlate PGE₂ enzyme immunoassay kit, Assay Designs, Inc.). Cyclooxygenase activity in the absence of test compounds is

- 26 -

determined as the difference in PGE₂ levels of cells challenged with AA versus the PGE₂ levels in cells mock-challenged with ethanol vehicle. Inhibition of PGE₂ synthesis by test compounds is calculated as a percentage of the activity in the presence of drug versus the activity in the positive control samples.

Assay of COX-1 Activity from U937 cell microsomes

U 937 cells are pelleted by centrifugation at 500 x g for 5 min and washed once with phosphate-buffered saline and repelleted. Cells are resuspended in homogenization buffer consisting of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2 µg/ml leupeptin, 2 µg/ml soybean trypsin inhibitor, 2 µg/ml aprotinin and 1 mM phenyl methyl sulfonyl fluoride. The cell suspension is sonicated 4 times for 10 sec and is centrifuged at 10,000 x g for 10 min at 4°C. The supernatant is centrifuged at 100,000 x g for 1 hr at 4°C. The 100,000 x g microsomal pellet is resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA to approximately 7 mg protein/ml and stored at -80°C.

Microsomal preparations are thawed immediately prior to use, subjected to a brief sonication, and then diluted to a protein concentration of 125 µg/ml in 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA, 0.5 mM phenol, 1 mM reduced glutathione and 1 µM hematin. Assays are performed in duplicate in a final volume of 250 µl. Initially, 5 µl of DMSO vehicle or drug in DMSO are added to 20 µl of 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA in wells of a 96-deepwell polypropylene titre plate. 200 µl of the microsomal preparation are then added and pre-incubated for 15 min at room temperature before addition of 25 µl of 1 M arachidonic acid in 0.1 M Tris-HCl and 10 mM EDTA, pH 7.4. Samples are incubated for 40 min at room temperature and the reaction is stopped by the addition of 25 µl of 1 N HCl. Samples are neutralized with 25 µl of 1 N NaOH prior to quantitation of PGE₂ content by radioimmunoassay (Dupont-NEN or Amersham assay kits). Cyclooxygenase activity is defined as the difference between PGE₂ levels in samples incubated in the presence of arachidonic acid and ethanol vehicle.

- 27 -

Assay of the activity of purified human COX-2

The enzyme activity is measured using a chromogenic assay based on the oxidation of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) during the reduction of PGG₂ to PGH₂ by COX-2 (Copeland et al. (1994) Proc. Natl. Acad. Sci. 91, 11202-11206).

Recombinant human COX-2 is purified from Sf9 cells as previously described (Percival et al (1994) Arch. Biochem. Biophys. 15, 111-118). The assay mixture (180 µL) contains 100 mM sodium phosphate, pH 6.5, 2 mM genapol X-100, 1 µM hematin, 1 mg/ml gelatin, 80-100 units of purified enzyme (One unit of enzyme is defined as the amount of enzyme required to produce an O.D. change of 0.001/min at 610 nm) and 4 µL of the test compound in DMSO. The mixture is pre-incubated at room temperature (22°C) for 15 minutes prior to initiation of the enzymatic reaction by the addition of 20 µL of a sonicated solution of 1 mM AA and 1 mM TMPD in assay buffer (without enzyme or hematin). The enzymatic activity is measured by estimation of the initial velocity of TMPD oxidation over the first 36 sec of the reaction. A non-specific rate of oxidation is observed in the absence of enzyme (0.007 - 0.010 O.D. /min) and is subtracted before the calculation of the % inhibition. IC₅₀ values are derived from 4-parameter least squares non-linear regression analysis of the log-dose vs % inhibition plot.

25 HUMAN WHOLE BLOOD ASSAY

Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE₂ production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS, which induces COX-

- 28 -

2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE₂ production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B₂ (TxB₂) via activation of COX-1. Thus, the effect of test compounds on TxB₂ levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE₂ after LPS induction (COX-2) and TxB₂ following blood clotting (COX-1) in the same assay.

Method

A. COX-2 (LPS-induced PGE₂ production)

- 15 Fresh blood is collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects have no apparent inflammatory conditions and have not taken any NSAIDs for at least 7 days prior to blood collection. Plasma is immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE₂). The remaining blood is incubated with LPS (100 µg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA (Phosphate buffered saline) for 5 minutes at room temperature. Five hundred µL aliquots of blood are incubated with either 2µL of vehicle (DMSO) or 2µL of a test compound at final concentrations varying from 10nM to 30µM for 24 hours at 37°C. At the end of the incubation, the blood is centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100µL aliquot of plasma is mixed with 400µL of methanol for protein precipitation. The supernatant is obtained and is assayed for PGE₂ using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE₂ to its methyl oximate derivative according to the manufacturer's procedure.

B. COX-1 (Clotting-induced TxB₂ production)

Fresh blood is collected into vacutainers containing no

- 29 -

anticoagulants. Aliquots of 500 μ L are immediately transferred to siliconized microcentrifuge tubes preloaded with 2 μ L of either DMSO or a test compound at final concentrations varying from 10nM to 30 μ M. The tubes are vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum is obtained by centrifugation (12,000 x g for 5 min.). A 100 μ L aliquot of serum is mixed with 400 μ L of methanol for protein precipitation. The supernatant is obtained and is assayed for TxB₂ using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

10

RAT PAW EDEMA ASSAY

Protocol

Male Sprague-Dawley rats (150-200 g) are fasted overnight and are given, po, either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line is drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_0) is measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarily with 50 μ L of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 μ g carrageenan per paw). Three hr later, the paw volume (V_3) is measured and the increases in paw volume ($V_3 - V_0$) are calculated. The animals are sacrificed by CO₂ asphyxiation and the absence or presence of stomach lesions scored. Data is compared with the vehicle-control values and percent inhibition calculated. All treatment groups are coded to eliminate observer bias.

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NSAID-INDUCED GASTROPATHY IN RATS

Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of COX-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDs. In fact, rat models have

- 30 -

been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal ^{51}Cr excretion after systemic injection of ^{51}Cr -labeled red blood cells. Fecal ^{51}Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of ^{51}Cr -labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water *ad lib*. Feces are collected for a 48 h period and ^{51}Cr fecal excretion is calculated as a percent of total injected dose. ^{51}Cr -labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 μ Ci of sodium ^{51}Cr chromate for 30 min. at 37°C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium ^{51}Cr chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 μ Ci) is injected per rat.

PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard non-steroidal anti-inflammatory drugs (NSAIDs). This can be quantitatively assessed by intravenous administration of $^{51}\text{CrCl}_3$ solution. This isotopic ion can

- 31 -

avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

5

Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocell or 5% Tween 80 in H₂O vehicles, (3mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous ⁵¹Cr (5μ Ci/kg in 1 ml/kg phosphate buffer saline (PBS)) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted ⁵¹Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

15

PHARMACOKINETICS IN RATS

Per Os Pharmacokinetics in Rats

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The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

Male Sprague Dawley rats (325-375 g) are fasted overnight prior to each PO blood level study.

25

The rats are placed in the restrainer one at a time and the box firmly secured. The zero blood sample is obtained by nicking a small (1 mm or less) piece off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top to the bottom to milk out the blood. Approximately 1 mL of blood is collected into a heparinized vacutainer tube.

30

Compounds are prepared as required, in a standard dosing ~~volume of 10mL/kg, and administered orally by passing a 16 gauge, 3"~~ gaging needle into the stomach.

Subsequent bleeds are taken in the same manner as the zero bleed except that there is no need to nick the tail again. The tail is

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- 32 -

cleaned with a piece of gauze and milked/stroked as described above into the appropriately labelled tubes.

- 5 Immediately after sampling, blood is centrifuged, separated, put into clearly marked vials and stored in a freezer until analysed.

Typical time points for determination of rat blood levels after PO dosing are:

0, 15min, 30min, 1h, 2h, 4h, 6h

- 10 After the 4 hr time point bleed, food is provided to the rats *ad libitum*. Water is provided at all times during the study.

Vehicles:

- 15 The following vehicles may be used in PO rat blood level determinations:

PEG 200/300/400: restricted to 2 mL/kg

Methocel 0.5% - 1.0%: 10mL/kg

- 20 Tween 80: 10mL/kg

Compounds for PO blood levels can be in suspension form. For better dissolution, the solution can be placed in a sonicator for approximately 5 minutes.

- 25 For analysis, aliquots are diluted with an equal volume of acetonitrile and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with UV detection. Quantitation is done relative to a clean blood sample spiked with a known quantity of drug. Bioavailability (F) is assessed by
30 comparing area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUC_{po} \times DOSE_{iv} \times 100\%}{AUC_{iv} \times DOSE_{po}}$$

- 35 Clearance rates are calculated from the following relation:

- 33 -

$$CL = \frac{DOSE_{iv}(mg/kg)}{AUC_{iv}}$$

The units of CL are mL/h•kg (milliliters per hour kilogram)

5

Intravenous Pharmacokinetics in Rats

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

10

Male Sprague Dawley (325-375 g) rats are placed in plastic shoe box cages with a suspended floor, cage top, water bottle and food.

The compound is prepared as required, in a standard dosing volume of 1 mL/kg.

15

Rats are bled for the zero blood sample and dosed under CO₂ sedation. The rats, one at a time, are placed in a primed CO₂ chamber and taken out as soon as they have lost their righting reflex. The rat is then placed on a restraining board, a nose cone with CO₂ delivery is placed over the muzzle and the rat restrained to the board with elastics. With the use of forceps and scissors, the jugular vein is exposed and the zero sample taken, followed by a measured dose of compound which is injected into the jugular vein. Light digital pressure is applied to the injection site, and the nose cone is removed. The time is noted. This constitutes the zero time point.

The 5 min bleed is taken by nicking a piece (1-2 mm) off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top of the tail to the bottom to milk the blood out of the tail. Approximately 1 mL of blood is collected into a heparinized collection vial. Subsequent bleeds are taken in the same fashion, except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and bled, as described above, into the appropriate labelled tubes.

30

Typical time points for determination of rat blood levels after I.V. dosing are either:

~~0, 5 min, 15min, 30min, 1h, 2h, 6h~~

or

0, 5 min, 30min, 1h, 2h, 4h, 6h.

- 34 -

Vehicles:

5 The following vehicles may be used in IV rat blood level determinations:

Dextrose: 1mL/kg
Muculosol 25%: 1mL/kg
10 DMSO (dimethylsulfoxide): Restricted to a dose volume of 0.1 mL per animal
PEG 200: Not more than 60% mixed with 40% sterile water - 1mL/kg

15 With Dextrose, either sodium bicarbonate or sodium carbonate can be added if the solution is cloudy.

For analysis, aliquots are diluted with an equal volume of acetonitrile and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with UV detection. Quantitation is done relative to a clean blood sample spiked
20 with a known quantity of drug. Bioavailability (F) is assessed by comparing area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUC_{po}}{AUC_{iv}} \times \frac{DOSE_{iv}}{DOSE_{po}} \times 100\%$$

25

Clearance rates are calculated from the following relation:

$$CL = \frac{DOSE_{iv}(mg/kg)}{AUC_{iv}}$$

30

The units of CL are mL/h•kg (milliliters per hour kilogram)

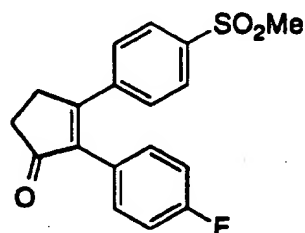
Representative Biological Data

35 Compounds of the present invention are inhibitors of COX-2 and are thereby useful in the treatment of COX-2 mediated diseases as

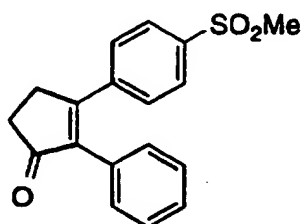
- 35 -

enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E₂ (PGE₂) synthesized in the presence of AA, COX-1 or COX-2 and a putative inhibitor. The IC₅₀ values represent the concentration of putative inhibitor required to lower PGE₂ synthesis to 50% of that obtained as compared to the uninhibited control.

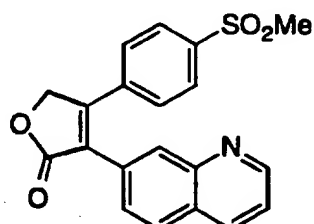
Data from three of these biological assays is given for representative compounds in Table II, along with comparative data for the following three compounds from U.S. Patent No. 5,474,995:

**A**

Ex. 7, Col 24, Line 60

**B**

Col. 41, Line 5

**C**

Ex. 50, Col. 32, Line 5

Table II

Example	Cox-2 Whole Blood (IC ₅₀ , μM)	Cox-1 U937 (IC ₅₀ , μM)	Selectivity Ratio	Rat Paw Edema (ED ₅₀ , mg/kg)
A	0.09	0.45	5	3.0
B	0.19	1.9	10	10
C	0.59	0.6	1	
1	0.58	30	52	1.7
2	0.89	>100	>112	
10	0.46	36	78	2.5

- 36 -

As can be seen from this data, the compounds of the present invention show greater COX-2 selectivity and/or potency than A, B, and C. The basicity of the pyridine ring in these examples also permits the formation of acid salts, resulting in increased water solubility and give
5 the potential for parenteral administration in aqueous vehicles.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- 10 (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C,
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-
15 30 mm. Hg) with a bath temperature of up to 60°C,
- (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;
- 20 (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points
25 in some preparations;
- (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR)
30 spectrometry or microanalytical data;
- (vi) yields are given for illustration only;
- (vii) when given, NMR data is in the form of delta (d)

- 37 -

values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)), r.t. (room temperature).

EXAMPLE 1

3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one

20 Step 1: 2-Bromo-2-cyclopenten-1-one

To a 0°C solution of 2-cyclopenten-1-one (125 g, 1.52 mol) in CCl₄ (1.2 L) in a three-neck flask equipped with an overhead stirrer was added a solution of bromine (269 g, 1.68 mol) in CCl₄ (400 mL) dropwise over 4 h, maintaining an internal temperature <2°C. A solution of Et₃N (310 mL, 2.22 mol) in CCl₄ (200 mL) was then added dropwise over 1.5 h, maintaining an internal temperature <10°C. The resulting suspension was warmed to r.t. for 1 h, then cooled to 0°C and filtered. The filtrate was washed with two 700 mL portions of 3M HCl and 500 mL of brine, then filtered through cotton. Concentration provided 228 g of an orange oil which was crystalized from 150 mL of 2:1 hexane: ether to provide 191 g of the title compound.

¹H NMR (CD₃COCD₃) δ 7.94 (1H, t), 2.72 (2H, m), 2.46 (2H, m).

35 Step 2: 2-Bromo-3-(4-(methylthio)phenyl)-2-cyclopenten-1-one

- 38 -

To a -78°C solution of 4-bromothioanisole (35.1 g, 173 mmol) in THF (500 mL) was added nBuLi (1.6 M in hexanes, 107.5 mL, 172 mmol). The solution was stirred for 45 min, then a solution of
5 2-bromo-2-cyclopenten-1-one (25.4 g, 158 mmol) in THF (150 mL) was added and the mixture was allowed to warm to 0°C and was quenched with saturated aqueous NH₄Cl. The majority of the solvent was removed *in vacuo* and the residue was suspended in water and extracted with two portions of EtOAc. The organic layers were washed
10 with brine, dried over MgSO₄, filtered and concentrated. This material was dissolved in DMF (300 mL), cooled to 0°C and treated with PDC (72.4 g, 192 mmol). The resulting mixture was warmed to r.t. and stirred for 2 h, then poured into H₂O (1.2 L) and extracted with two
15 500 mL portions of EtOAc. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to give the title compound as a light brown solid which was used directly in the next step.

Step 3: 2-Bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one
20

To a 0°C solution of 2-bromo-3-(4-(thiomethyl)phenyl)-2-cyclopenten-1-one in 2:1 CH₂Cl₂/MeOH (500 mL) was added MMPP (100 g). The mixture was stirred at r.t. overnight, then concentrated and partitioned between saturated NaHCO₃, 1M Na₂S₂O₃ and CH₂Cl₂.
25 The aqueous layer was extracted with CH₂Cl₂, and the combined organics were washed with brine, filtered through cotton and evaporated. The resulting solid was swished in CH₂Cl₂/Et₂O to provide 23 g of the title compound.

30 ¹H NMR (CD₃COCD₃) δ 8.12 (4H, m), 3.22 (2H, m), 3.20 (3H, s), 2.69 (2H, m).

Step 4: Lithium 3-pyridinyltrimethyl boronate

To a -88°C solution of 3-bromopyridine (10.1 mL, 104.8 mmol) in Et₂O (450 mL) was added a 1.6 M hexane solution of n-BuLi
35

- 39 -

(66 mL, 105.6 mmol). The reaction mixture was warmed to -78 °C for 1 h to give a thick yellow slurry. Triisopropyl borate (26 mL, 112.7 mmol) was then added to give a slight exotherm (-78°C to -63°C) and a clear solution. The mixture was stirred at -78°C for 15 min, then
5 warmed to r.t. and concentrated to dryness. The residue was dissolved in MeOH and concentrated three times to give 27.2 g of pyridin-3-yl-trimethyl lithium boronate. This material was used in the next step without further purification.

10 ¹H NMR (CD₃OD, 400 MHz) δ 7.15 (1H, m), 7.85 (1H, m), 8.15 (1H, m), 8.50 (1H, m)

Step 5: 3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one

15 To a mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (3.37 g, 10.7 mmol), lithium 3-pyridinyltrimethyl boronate (3.43 g, 18.2 mmol), Pd₂(dba)₃ (0.196 g, 0.214 mmol), and PPh₃ (0.224 g, 0.855 mmol) was added toluene (75 mL), n-propanol (25 mL), and H₂O (25 mL). The mixture was degassed and stirred
20 under N₂ for 15 min then heated to reflux. After 4 h, the reaction mixture was cooled to r.t., diluted with 100 mL of CH₂Cl₂ and washed with H₂O. The aqueous layer was separated and washed 3 times with 100 mL of CH₂Cl₂. The organic layers were combined, washed with brine and filtered through cotton. The filtrate was concentrated to
25 dryness and the residue was purified by flash chromatography (100 % EtOAc) followed by swishing in a mixture of CH₂Cl₂ and Et₂O to provide 2.6 g of the title compound.

30 ¹H NMR (CDCl₃) δ 8.55 (1H, m), 8.34 (1H, m), 7.40 (2H, m), 7.65 (1H, m), 7.49 (2H, m), 7.33 (1H, m), 3.12 (2H, m), 3.05 (3H, s), 2.80 (2H, m).

~~Step 6:~~ 3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one hydrochloride

35 To a solution of 3-(4-(methylsulfonyl)phenyl)-2-(3-

- 40 -

pyridinyl)-2-cyclopenten-1-one (5.0 g, 15.96 mmol) in CH₂Cl₂ (50 mL) was passed a stream of HCl gas for 10 min. Excess HCl was removed by bubbling a stream of air through the solution. The solution was then concentrated and swished in Et₂O to give 5.7 g of the title compound.

5

¹H NMR (CDCl₃) δ 8.70 (1H, m), 8.52 (1H, m), 8.38 (1H, m), 8.00 (2H, m), 7.94 (1H, m), 7.50 (2H, m), 3.20 (2H, m), 3.13 (3H, s), 2.85 (2H, m).

10 Step 7: 3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one hydromethanesulfonate

To a solution of 3-(4-(methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-1-one (104 mg, 0.33 mmol) in CH₂Cl₂ (50 mL) was added methanesulfonic acid (0.02 mL, 0.32 mmol) and the solution was concentrated to give a foam. The foam was swished in Et₂O to give 108 mg of the title compound as an off-white solid.

15

EXAMPLE 2

20 2-(5-Chloropyridin-3-yl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

Step 1: Trifluoromethanesulfonic acid 5-chloro-3-pyridinyl ester

To a -78°C solution of 5-chloro-3-hydroxypyridine (1.0 g, 7.72 mmol) and diisopropylethyl amine (1.88 mL, 10.81 mmol) in CH₂Cl₂ (35 mL) was added trifluoromethanesulfonic anhydride (1.55 mL, 9.26 mmol) slowly to give a dark red solution. After 1 mL of trifluoromethanesulfonic anhydride was added, a precipitate formed and the mixture became hard to stir. The mixture was immersed in a -10°C bath and the rest of the trifluoromethanesulfonic anhydride was added. After 15 min, the mixture was washed with H₂O and brine, filtered through cotton and concentrated to dryness. The residue was purified by flash chromatography (10 % EtOAc/ hexanes) to give 510 mg of the title compound.

35

- 41 -

^1H NMR (CD_3COCD_3) δ 8.75 (2H, m), 8.20 (1H, m).

Step 2: 3-Trimethylstannanyl-5-chloropyridine

To a mixture of $\text{Pd}_2(\text{dba})_3$ (0.038 g, 0.04 mmol) and PPh_3 (0.086 g, 0.33 mmol) was added dioxane (2 mL). The resulting suspension was degassed and stirred at r.t. for fifteen minutes before it was transferred via cannula into a degassed r.t. mixture of trifluoromethanesulfonic acid 5-chloro-3-pyridinyl ester (0.510 g, 2.06 mmol), hexamethylditin (0.443 mL, 2.16 mmol), LiCl (0.262 g, 6.18 mmol), and a few crystals of BHT. The resulting mixture was heated to reflux for 2.5 h, then cooled to r.t., diluted with EtOAc, washed with 10% NH_4OH and brine, dried over MgSO_4 , filtered, and concentrated to dryness. The residue was used in step 3 without further purification.

Step 3: 2-(5-Chloro-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a degassed r.t. solution of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (0.630 g, 2.0 mmol), $\text{Pd}_2(\text{dba})_3$ (0.037 g, 0.04 mmol), and AsPh_3 (0.098 g, 0.32 mmol) in 5 mL NMP was added a degassed NMP solution (5 mL) of 3-trimethylstannanyl-5-chloropyridine (~2.0 mmol). The resulting mixture was heated to 60°C for 16 h. The mixture was then cooled to r.t., diluted with EtOAc, washed with water and brine, dried over MgSO_4 , and concentrated to dryness. The residue was purified by flash chromatography (80 % EtOAc/ hexanes) followed by a $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ swish to provide 0.215 g of the title compound.

^1H NMR (CD_3COCD_3) δ 8.50 (1H, d), 8.20 (1H, d), 7.95 (2H, m), 7.22, (1H, dd), 7.18 (2H, m), 3.22 (2H, m), 3.16 (3H, s), 2.71 (2H, m).

EXAMPLE 3

2-(5-Bromo-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

- 42 -

Step 1: Lithium 5-bromo-3-pyridinyltrimethyl boronate

To a -105°C solution of 3,5-dibromopyridine (2.00 mL, 8.44 mmol) in Et₂O (40 mL) was added a 1.6 M solution of n-BuLi (5.54 mL, 8.86 mmol). The reaction mixture was allowed to stir at -105°C for five minutes to give a yellow precipitate. Triisopropyl borate (3.90 mL, 16.88 mmol) was then added and the reaction mixture was allowed to warm to r.t. The residue was diluted with MeOH and concentrated three times to give a white solid which was used in the next step without further purification.

Step 2: 2-(3-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (0.500 g, 1.59 mmol), lithium 5-bromo-3-pyridinyltrimethyl boronate (0.729 g, 3.17 mmol), Pd₂(dba)₃ (0.044 g, 0.048 mmol), and PPh₃ (0.050 g, 0.190 mmol) was added toluene (15 mL), n-propanol (5 mL), and H₂O (5 mL). The mixture was degassed and stirred under N₂ for 15 min before diethyl amine (0.427 mL, 4.12 mmol) was added and the mixture was heated to reflux. After three hours, the reaction mixture was cooled to r.t., diluted with CH₂Cl₂ and washed with H₂O. The H₂O was separated and washed 3 times with CH₂Cl₂. The organic layers were combined, washed with brine and filtered through cotton. The filtrate was concentrated to dryness and the residue was purified by flash chromatography (75% ETOAc/ hexanes) followed by a CH₂Cl₂/Et₂O swish, to yield 0.160 g of the title compound.

¹H NMR (CD₃COCD₃) δ 8.60 (1H, d), 8.25 (1H, d), 7.96 (2H, m), 7.37 (1H, dd), 7.69 (2H, m), 3.22 (2H, m), 3.14 (3H, s), 2.73 (2H, m).

EXAMPLE 4**2-(2-Methyl-5-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one**

- 43 -

Step 1: Trifluoromethanesulfonic acid 2-methyl-5-pyridinyl ester

To a -78°C solution of 2-methyl-5-hydroxypyridine (1.0 g, 9.16 mmol) and diisopropylethyl amine (2.23 mL, 12.83 mmol) in CH₂Cl₂ (50 mL) was added trifluoromethanesulfonic anhydride (1.85 mL, 11.0 mmol). The reaction mixture was then allowed to warm to r.t. After 30 min, the mixture was washed with water and brine, filtered through cotton and concentrated to dryness. The residue was purified by flash chromatography (12.5 % EtOAc/hexanes) to give 0.483 g of the title compound.

¹H NMR (CD₃COCD₃) δ 8.57 (1H, d), 7.80 (1H, dd), 7.47 (1H, d), 2.55 (3H, s).

Step 2: 5-Trimethylstannanyl-2-methylpyridine

To a mixture of Pd₂(dba)₃ (0.047 g, 0.04 mmol), and PPh₃ (0.085 g, 0.32 mmol) was added dioxane (2 mL). The resulting suspension was degassed and stirred at r.t. for 15 min before it was transferred via cannula into a degassed r.t. dioxane suspension (8 mL) of trifluoromethanesulfonic acid 2-methyl-5-pyridinyl ester (0.460 g, 2.02 mmol), hexamethylditin (0.435 mL, 2.13 mmol), LiCl (0.257 g, 6.07 mmol), and a few crystals of BHT. The resulting mixture was heated to reflux for 2.5 h before it was cooled to r.t., diluted with CH₂Cl₂, washed with 10 % NH₄OH and brine, filtered through cotton, and concentrated to dryness. The residue was used in step 3 without further purification.

Step 3: 2-(2-Methyl-5-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a degassed r.t. solution of 2-bromo-3-(4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one (0.315 g, 1.0 mmol), Pd₂(dba)₃ (0.018 g, 0.02 mmol), and AsPh₃ (0.049 g, 0.16 mmol) in NMP (2.5 mL) was added a degassed NMP solution (2.5 mL) of 5-trimethylstannanyl-2-methylpyridine (~2.0 mmol). The resulting mixture was heated to 60 °C for 16 hours, then to 100°C for a further 3.5 h. The mixture was then cooled to r.t., diluted with EtOAc, washed

- 44 -

2 times with 10% NH₄OH and brine, dried over MgSO₄, and concentrated to dryness. The residue was purified by flash chromatography (100 % EtOAc/ hexanes) to provide 0.070 g of the title compound as a rigid foam.

5

¹H NMR (CD₃COCD₃) δ 8.20 (1H, d), 7.94 (2H, m), 7.65 (2H, m), 7.47 (1H, dd), 7.20 (1H, d), 3.18 (2H, m), 3.14 (3H, s), 2.69 (2H, m).

EXAMPLE 5

10

2-(2-Methoxy-5-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

Step 1: 5-Bromo-2-methoxypyridine

15

To a solution of 2,5-dibromopyridine (1.4 g, 5.9 mmol) in DMF (10mL) was added MeOH (4 mL), and 8N aqueous KOH (1 mL). The solution was heated to 100°C for 2 h, then cooled and partitioned between Et₂O and H₂O. The organic layer was washed with brine, dried over MgSO₄ and concentrated to provide 840 mg of the title compound, which was used in the next step without further purification.

20

Step 2: Lithium 2-methoxy-5-pyridinyltrimethyl boronate

25

To a -78°C solution of the total sample of 5-bromo-2-methoxypyridine from Step 1 in Et₂O (20 mL) was added a 1.6 M solution of n-BuLi (3.5 mL, 5.6 mmol). The reaction mixture was allowed to stir 10 min to give an orange suspension. Triisopropyl borate (1.5 mL, 6.5 mmol) was then added and the reaction mixture was allowed to warm to r.t. The residue was diluted with MeOH and concentrated three times to give a white solid which was used in the next step without further purification.

30

Step 3: 2-(2-Methoxy-5-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

35

A mixture of the total sample of lithium 2-methoxy-5-pyridinyltrimethyl boronate from Step 2, 2-bromo-3-(4-

- 45 -

(methylsulfonyl)phenyl)-2-cyclopenten-1-one (400 mg, 1.3 mmol), Pd₂(dba)₃ (70 mg, 0.08 mmol) and PPh₃ (83 mg, 0.32 mmol) was dissolved in 3:1:1 toluene: n-propanol: H₂O (50 mL) and degassed. The solution was stirred 10 min at r.t., heated to reflux for 2.5 h, then
5 cooled and concentrated in vacuo. The residue was partitioned between CH₂Cl₂ and aqueous NaHCO₃. The organic phase was washed with brine, filtered through cotton and concentrated. Purification by flash chromatography (60% EtOAc/hexanes) provided 317 mg of an oil which was crystalized from EtOAc/hexanes to give 230 mg of the title
10 compound.

¹H NMR (CD₃COCD₃, 300 MHz) δ 7.95 (3H, m); 7.68 (2H, m); 7.48 (1H, dd); 6.72 (1H, dd), 3.87 (3H, s), 3.14 (2H, m), 3.12 (3H, s), 2.68 (2H, m).
15

EXAMPLE 9

2-(2-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

20 Step 1: Trifluoromethanesulfonic acid 2-pyridinyl ester
To a -78°C solution of 2-hydroxypyridine (1.0 g, 10.5 mmol) and diisopropylethyl amine (2.56 mL, 14.7 mmol) in CH₂Cl₂ (40 mL) was added trifluoromethanesulfonic anhydride (2.12 mL, 12.6 mmol). The reaction mixture was then allowed to warm to r.t.. After
25 25 min, the mixture was washed with H₂O and brine, filtered through cotton and concentrated to dryness. The residue was purified by flash chromatography (9 % EtOAc/hexanes) to give 1.60 g of the title compound.

30 ¹H NMR (CD₃COCD₃) δ 8.46 (1H, m), 8.18 (1H, m), 7.62 (1H, m), 7.49 (1H, d).

Step 2: 2-Trimethylstannanyl pyridine

To a mixture of Pd₂(dba)₃ (0.129 g, 0.14 mmol), and PPh₃
35 (0.296 g, 1.13 mmol) was added dioxane (6 mL). The resulting

- 46 -

suspension was degassed and stirred at r.t. for 15 min before it was transferred via cannula into a degassed r.t. suspension of trifluoromethanesulfonic acid 2-pyridinyl ester (1.6 g, 7.04 mmol), hexamethylditin (1.51 mL, 7.40 mmol), LiCl (0.895 g, 21.1 mmol), and
5 a few crystals of BHT in dioxane (23 mL). The resulting mixture was heated to reflux for 3 h before it was cooled to room temperature, diluted with CH₂Cl₂, washed with 10% NH₄OH and brine, filtered through cotton, and concentrated to dryness. The residue was used in step 3 without further purification.

10

Step 3: 2-(2-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a degassed r.t. solution of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (1.103 g, 3.5 mmol),
15 Pd₂(dba)₃ (0.064 g, 0.07 mmol), and AsPh₃ (0.171 g, 0.56 mmol) in NMP (7.5 mL) was added a degassed NMP solution (10 mL) of 2-trimethylstannanyl pyridine (~7.0 mmol). The resulting mixture was heated to 100°C for 16 hours. The mixture was then cooled to r.t., diluted with EtOAc, washed 3 times with 10% NH₄OH and brine, dried
20 over MgSO₄, and concentrated to dryness. The residue was purified by flash chromatography (5% MeOH/ EtOAc) to provide 0.215 g of the title compound.

¹H NMR (CD₃COCD₃) δ 8.46 (1H, m), 7.88 (2H, m), 7.80 (1H, m),
25 7.62 (2H, m), 7.45 (1H, m), 7.30 (1H, m), 3.21 (2H, m), 3.12 (2H, m), 2.71 (2H, m).

EXAMPLE 10

30 2-(5-Chloro-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

Step 1: Trifluoromethanesulfonic acid 5-chloro-2-pyridinyl ester

To a -78°C solution of 5-chloro-2-hydroxypyridine (1.0 g,
35 7.72 mmol) and diisopropylethyl amine (1.88 mL, 10.81 mmol) in

- 47 -

CH₂Cl₂ (35 mL) was added trifluoromethanesulfonic anhydride (1.56 mL, 9.26 mmol), and the reaction mixture was allowed to warm to r.t. After 30 min, the mixture was washed with H₂O and brine, filtered through cotton and concentrated to dryness. The residue was purified by flash chromatography (8 % EtOAc/hexanes) and to give 1.0 g of the title compound.

¹H NMR (CD₃COCD₃) δ 8.50 (1H, d), 8.23 (1H, dd), 7.58 (1H, d).

10 Step 2: 2-Trimethylstannanyl-5-chloropyridine

To a degassed room temperature mixture of trifluoromethanesulfonic acid 5-chloro-3-pyridinyl ester (0.510 g, 2.06 mmol), hexamethylditin (0.443 mL, 2.16 mmol), LiCl (0.262 g, 6.18 mmol), and a few crystals of BHT were added a freshly prepared solution of 0.1 M solution of Pd(PPh₃)₄ in toluene (0.807 mL, 0.081 mmol). The resulting mixture was heated to reflux for 1.5 h before it was cooled to r.t., diluted with EtOAc, washed with 10 % NH₄OH and brine, dried over MgSO₄, filtered, and concentrated to dryness. The residue was used in step 3 without further purification.

20 Step 3: 2-(5-Chloro-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

To a degassed r.t. solution of 2-bromo-3-(4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one (0.630 g, 2.0 mmol), Pd₂(dba)₃ (0.036 g, 0.04 mmol), and AsPh₃ (0.098 g, 0.32 mmol) in NMP (5 mL) was added a degassed NMP solution (8 mL) of 2-trimethylstannanyl-5-chloropyridine (~4.0 mmol). The resulting mixture was heated to 60°C for 16 h, then to 100°C for a further 2 h. The mixture was then cooled to r.t., diluted with EtOAc, washed 2 times with 10% NH₄OH and brine, dried over MgSO₄, and concentrated to dryness. The residue was purified by flash chromatography (70% EtOAc/hexanes) followed by a CH₂Cl₂/Et₂O swish to provide 130 mg of the title compound.

35 ¹H NMR (CD₃SOCD₃) δ 8.54 (1H, d), 8.00 (1H, dd), 7.39 (2H, m),

- 48 -

7.55 (2H, m), 7.45 (1H, d), 3.23 (3H, s), 3.13 (2H, m), 2.69 (2H, m).

EXAMPLE 12

5 2-(5-Bromo-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

Step 1: 2-Trimethylstannanyl-5-bromopyridine

10 A mixture of 2,5-dibromopyridine (1.42 g, 6.0 mmol), Pd₂(dba)₃ (178 mg, 0.19 mmol) and PPh₃ (315 mg, 1.20 mmol) was dissolved in dioxane (15 mL) and degassed. After 10 min at r.t., hexamethylditin (1.4 mL, 6.8 mmol) was added and the mixture was heated to reflux for 1.5 h, then cooled to r.t. The mixture was partitioned between saturated aqueous NaHCO₃ and CH₂Cl₂. The organic phase was washed with brine, filtered through cotton and concentrated. The residue was used directly in step 2 without further purification.

20 Step 2: 2-(5-Bromo-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

25 A mixture of 2-bromo-3-(4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one (700 mg, 2.2 mmol), Pd₂(dba)₃ (170 mg, 0.18 mmol), and the total sample of 2-trimethylstannanyl-5-bromopyridine from Step 1 was dissolved in NMP (10 mL) and degassed. The resulting solution was heated to 100°C for 3.5 h then cooled. The mixture was diluted with EtOAc, washed 2 times with 10% NH₄OH and brine, dried over MgSO₄, and concentrated. The residue was purified by flash chromatography (70 % EtOAc/hexanes) followed by an EtOAc/ Et₂O swish to provide 110 mg of the title compound.

30 ¹H NMR (CDCl₃, 300 MHz) δ 8.59 (1H, d), 7.90 (3H, m), 7.48 (2H, m), 7.40 (1H, d), 3.12 (2H, m), 3.06 (3H, s), 2.80 (2H, m).

EXAMPLE 16

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- 49 -

2-(4-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-oneStep 1: Lithium 4-pyridinyltrimethyl boronate

To a -107°C solution of 4-bromopyridine (1.77 g, 11.20 mmol) in Et₂O (50 mL) was added a 1.6 M solution of n-BuLi (5.54 mL, 8.86 mmol). The reaction mixture was allowed to stir at -105°C for five minutes. Triisopropyl borate (3.62 mL, 15.68 mmol) was then added and the reaction mixture was then allowed to warm to r.t. The reaction mixture was diluted with MeOH and concentrated three times to give a white solid which was used in the next step without further purification.

¹H NMR (CD₃OD, 400 MHz) δ 8.19 (2H, m), 7.47 (2H, m)

Step 2: 2-(4-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one

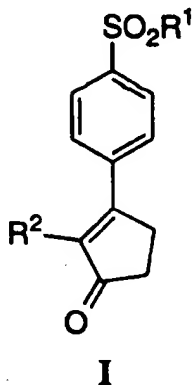
To a mixture of 2-bromo-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one (0.500 g, 1.59 mmol), lithium 4-pyridinyltrimethyl boronate (0.480 g, 2.54 mmol), Pd₂(dba)₃ (0.029 g, 0.03 mmol), and PPh₃ (0.033 g, 0.13 mmol) was added toluene (15 mL), n-propanol (5 mL), and H₂O (5 mL). The mixture was degassed and stirred under N₂ for 15 min before it was heated to reflux. After 3.5 h, the reaction mixture was cooled to r.t., diluted with CH₂Cl₂, washed with H₂O and brine, and filtered through cotton. The filtrate was concentrated to dryness and the residue was purified by flash chromatography (5 % MeOH/EtOAc) followed by a CH₂Cl₂/Et₂O swish, to yield 0.130 g of the title product.

¹H NMR (CD₃COCD₃) δ 8.53 (2H, m), 7.95 (2H, m), 7.63 (2H, m), 7.15 (2H, m), 3.20 (2H, m), 3.14 (3H, s), 2.71 (2H, m).

- 50 -

WHAT IS CLAIMED IS:

1. A compound of Formula I



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or a pharmaceutically salt thereof wherein:

 R^1 is selected from the group consisting of

- (a) CH_3 ,
- (b) NH_2 ,
- 10 (c) $NHC(O)CF_3$,
- (d) $NHCH_3$;

 R^2 is a mono-, di-, or tri-substituted pyridinyl, wherein the substituents are chosen from the group consisting of

- (a) hydrogen,
- 15 (b) halo,
- (c) C1-6alkoxy,
- (d) C1-6alkylthio,
- (e) CN,
- (f) C1-6alkyl,
- 20 (g) C1-6fluoroalkyl,
- (h) N_3 ,
- (i) $-COOR^3$,
- (j) hydroxy,
- (k) $-C(R^3)(R^4)-OH$,
- 25 (l) $-C1-6alkyl-CO_2-R^3$,
- (m) C1-6fluoroalkoxy;

 R^3 and R^4 are independently chosen from the group consisting of

- (a) hydrogen,

- 51 -

(b) C₁-6alkyl,
or R³ and R⁴ together with the carbon to which they are attached form
a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

5 2. A compound according to Claim 1 wherein R² is a
mono-, di-, or trisubstituted 2-pyridinyl.

 3. A compound according to Claim 1 wherein R² is a
mono-, di-, or trisubstituted 3-pyridinyl.

10 4. A compound according to Claim 1 wherein R¹ is
CH₃ or NH₂.

 5. A compound according to Claim 1 wherein R² is a
15 mono-, di-, or trisubstituted 2-pyridinyl or 3-pyridinyl and the
substituents are selected from the group consisting of

- (a) hydrogen,
 (b) halo,
 (c) C₁-6alkoxy,
20 (d) C₁-6alkylthio,
 (e) C₁-6alkyl,
 (f) CF₃,
 (g) CN.

25 6. A compound according to Claim 1 wherein R¹ is
CH₃ or NH₂.

 R² is a mono-, di-, or trisubstituted 2-pyridinyl or 3-
pyridinyl and the substituents are selected from the group consisting of

- (a) hydrogen,
30 (b) halo,
 (c) C₁-6alkoxy,
 (d) C₁-6alkylthio,
 (e) C₁-6alkyl,
 (f) CF₃,
35 (g) CN.

- 52 -

7. A compound selected from the group consisting of

- 5 1-one,
(a) 3-(4-(Methylsulfonyl)phenyl)-2-(3-pyridinyl)-2-cyclopenten-
(b) 2-(5-Chloropyridin-3-yl)-3-(4-(methylsulfonyl)-phenyl)-2-
cyclopenten-1-one,
(c) 2-(5-Bromo-3-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-
cyclopenten-1-one,
10 (d) 2-(2-Methyl-5-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-
cyclopenten-1-one,
(e) 2-(2-Methoxy-5-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-
cyclopenten-1-one,
(f) 2-(2-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-
15 1-one,
(g) 2-(5-Chloro-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-
cyclopenten-1-one,
(h) 2-(5-Bromo-2-pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-
cyclopenten-1-one,
20 (i) 2-(4-Pyridinyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-
one, or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 7 wherein the
pharmaceutically acceptable salt is an acid salt of citric, hydrobromic,
25 hydrochloric, maleic, methanesulfonic, phosphoric, sulfuric or tartaric
acid.

9. A compound according to Claim 8 wherein the
pharmaceutically acceptable salt is an acid salt of hydrochloric or
methanesulfonic acid.

30 10. A pharmaceutical composition for treating an
inflammatory disease susceptible to treatment with an non-steroidal anti-
inflammatory agent comprising:
a non-toxic therapeutically effective amount of a compound according
to any one of Claims 1 to 9, and a pharmaceutically acceptable carrier.

35

11. A pharmaceutical composition for treating

- 53 -

cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

- 5 a non-toxic therapeutically effective amount of a compound according to any one of Claims 1 to 9, and a pharmaceutically acceptable carrier.

12. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:

- 10 administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

13. A method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

15 administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.

14. A pharmaceutically acceptable salt of a compound of formula (I), as defined in any one of claims 1 to 6.

15. A compound of formula (I) according to claim 1, 2, 3, 4, 5 or 6, or a pharmaceutically acceptable salt thereof for use in the treatment of inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

16. A compound or salt according to claim 7, 8 or 9, for use in the treatment of cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1.

17. Use of a compound or salt according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00270

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/50 C07D213/61 C07D213/64 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 00501 A (MERCK FROSST CANADA INC ;DUCHARME YVES (CA); GAUTHIER JACQUES YVES) 5 January 1995 cited in the application see the whole document ---	1-17
E	WO 97 16435 A (MERCK FROSST CANADA INC ;BLACK CAMERON (CA); LEGER SERGE (CA); PRA) 9 May 1997 see the whole document -----	1-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search 15 July 1997	Date of mailing of the international search report 23.07.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Bosma, P

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 97/00270

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 12, 13
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 97/00270

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WO 9716435 A	09-05-97	NONE	
